UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

November 7, 2011

MEMORANDUM

Subject:	Name of Pesticide Product:	DUPONT IMAZAPYR II 75 XP HERBICIDE
	EPA Reg. No. /File Symbol:	352-ILL
	DP Barcode:	DP 390860
	Decision No.:	450086
	Action Code:	R310
	PC Code:	128821 (Imazapyr: 75%)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
Nov. 7, 2011

M Hashim
Team Leader/Tox

To: Maggie Rudick/Kable Davis RM 25
Herbicide Branch
Registration Division (7505P)

Registrant: E.I. DU PONT DE NEMOURS AND CO., INC.

FORMULATION FROM LABEL:

Active Ingredient(s):		by wt.
128821 Imazapyr		75.0%
Other Ingredients:		25.0%
	TOTAL	100.0%

ACTION REQUESTED: The Risk Manager requests:

"…Please review attached acute toxicity studies. I've attached the cover letter, CDFs (basic and 1 alt), and proposed label…"

BACKGROUND:

The material received for review includes a set of 6 acute toxicity studies (MRIDs 48499404-48499409), a proposed label (with the signal word CAUTION), and basic and alternate CSFs (both dated June 14, 2011), and a cover letter dated June 1, 2011.

COMMENTS AND RECOMMENDATIONS:

1. A contractor (Summitec Corporation) did the primary reviews on the six acute toxicity studies and produced a DER for each study; TRB did secondary reviews on the DERs, making revisions where appropriate.

2. All six of the acute toxicity studies have been classified as acceptable. These studies satisfy the acute toxicity data requirements for the registration of EPA File Symbol 352-ILL [DuPont™ Imazapyr II 75XP].

3. The following is the acute toxicity profile for EPA File Symbol 352-ILL, based on the results of the acute toxicity studies:

Acute oral toxicity	IV	Acceptable	MRID 48499404
Acute dermal toxicity	IV	Acceptable	MRID 48499405
Acute inhalation toxicity	IV	Acceptable	MRID 48499406
Primary eye irritation	III	Acceptable	MRID 48499407
Primary dermal irritation	IV	Acceptable	MRID 48499408
Dermal sensitization	No	Acceptable	MRID 48499409

4. Based on the acute toxicity profile above, and taking into consideration the proposed uses specified on the label and information in the CSF, the following would be the precautionary and first aid labeling for EPA File Symbol 352-ILL as obtained from the Label Review System:

PRODUCT ID #: **000352-00855**

PRODUCT NAME: **DUPONT™ IMAZAPYR II 75XP**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Causes moderate eye irritation. Avoid contact with eyes or clothing. Wear protective eyewear. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Wear: Long-sleeved shirt and long pants, Socks, Shoes, and chemical-resistant gloves (such as Natural Rubber, Selection Category A).

First Aid:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

5. The registrant has proposed precautionary labeling addressing dermal and inhalation toxicity, as well as first aid statements for dermal, oral and inhalation exposure. These statements are acceptable.

6. The TRB Chemistry Team should review and accept the basic and alternate CSFs (both dated June 14, 2011).

DATA EVALUATION RECORD

IMAZAPYR
[IMAZAPYR 75SG]

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 425]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - MOUSE [OPPTS 870.2600; OECD 429]
MRID: 48499404, 48499405, 48499406, 48499407, 48499408, and 48499409

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 3-B-47

Primary Reviewer:
Donna L. Fefee, D.V.M.

Signature: Donna L. Fefee, AE
Date: AUG 2 6 2011

Secondary Reviewers:
Thomas C. Marshall, Ph.D., D.A.B.T.

Signature: Thomas C. Marshall, AE
Date: AUG 2 6 2011

Robert H. Ross, M.S., Program Manager

Signature: Robert H. Ross
Date: AUG 2 6 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: AUG 2 6 2011

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; EPSL Reference No.: 101207-1D; Off-white solid; specific gravity: 0.733 g/mL; pH: ~5 (1% aqueous solution); expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Lowe, C. (2011) Imazapyr (DPX-A7586) 75SG: acute oral toxicity up and down procedure in rats. Study Number 31314. Unpublished study prepared by Eurofins PSL, Dayton, New Jersey. April 22, 2011. MRID 48499404.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 48499404), three fasted, female, Sprague-Dawley-derived albino rats were given single oral gavage doses of ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] as a 65% w/w mixture in distilled water at a dose level of 5000 mg/kg bw, with dose selection, progression, and stopping criterion in accordance with a limit test under OECD 425. The animals were treated on day 0 and observed for up to 14 days. The animals were 9-10 weeks old, weighed 152-168 g, and were supplied by Ace Animals, Inc., Boyertown, Pennsylvania.

There were no deaths or abnormal gross necropsy findings, and all of the animals gained weight during both weeks of the study. The only abnormal clinical sign was red facial staining on one animal 1-5 hours after dosing.

LD_{50} Females > 5000 mg/kg bw

Based on the acute oral LD_{50} in females, Imazapyr 75SG is in EPA Toxicity Category IV.

This acute oral study is classified as Acceptable. It satisfies the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION: Individual animals were dosed as follows:

Animal No.	Dose level (mg/kg)	Short-Term Outcome	Long-Term Outcome
3101	5000	S	S
3102		S	S
3103		S	S

S = survival D = death

Due to the absence of mortality of the initial animal, the next two animals were dosed simultaneously.

Statistics: Statistical evaluation of results and calculation of LD_{50} are not required under OPPTS 870.1100 and were not done. Dose selection rationale, the assumed or expected LD_{50}, and the assumed sigma (or slope of the dose response curve) were not provided.

A. Mortality: There were no deaths.

B. Clinical observations: All three animals gained weight during both weeks of the study. The only abnormal clinical sign was red facial staining on one animal 1-5 hours after dosing.

C. Gross Necropsy: There were no abnormal findings.

D. Reviewer's Conclusions: In agreement with the study author, the acute oral LD_{50} for females is greater than 5000 mg/kg bw. This places the test material in EPA Toxicity Category IV.

E. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; EPSL Reference No.: 101207-1D; Off-white solid; specific gravity: 0.733 g/mL; pH: ~5 (1% aqueous solution); expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Lowe, C. (2011) Imazapyr (DPX-A7586) 75SG: acute dermal toxicity study in rats. Study Number 31315. Unpublished study prepared by Eurofins PSL, Dayton, New Jersey. April 22, 2011. MRID 48499405.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 48499405), a group of five male and five female Sprague-Dawley-derived albino rats was dermally exposed for 24 hours to ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] as a 75% w/w mixture in distilled water at a dose of 5000 mg/kg bw. The doses were applied to clipped application sites on the dorsal trunk, measuring approximately 2 inches by 3 inches (~10% of the body surface area) and covered by a 4-ply gauze pad secured with 3-inch Durapore tape wrapped around the trunk. The day of application was considered to be day 0, and the animals were observed for 14 days. The animals were 8-9 weeks old (males: 249-271 g, females: 175-196 g) and supplied by Ace Animals, Inc., Boyertown, Pennsylvania.

There were no deaths, abnormal gross necropsy findings, or abnormal clinical signs, including signs of local irritation at the application sites. All of the animals gained weight during both weeks of the study.

LD_{50} Males > 5000 mg/kg bw
LD_{50} Females: > 5000 mg/kg bw
LD_{50} Combined > 5000 mg/kg bw

Based on the acute dermal LD_{50} for males, females, and the combined sexes, Imazapyr 75SG is in EPA Toxicity Category IV.

This acute dermal study is classified as Acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

Statistics: Statistical evaluation of results is not required under OPPTS 870.1200 and was not done as part of this study.

A. Mortality: There were no deaths.

B. Clinical observations: There were no abnormal systemic clinical signs or signs of local dermal irritation at the dose sites. All of the animals gained weight during both weeks of the study.

C. Gross Necropsy: There were no abnormal findings.

D. Reviewer's Conclusions: In agreement with the study author, the acute dermal LD_{50} for males, females, and the combined sexes is greater than 5000 mg/kg bw. This places the test material in EPA Toxicity Category IV.

E. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Acute Inhalation Toxicity - Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; Haskell Reference No.: 29912; solid particulate with median particle size of 1.92 microns; expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Ng, S. (2011) Imazapyr (DPX-A7586) 75SG: inhalation median lethal concentration (LC_{50}) study in rats. Study Number 31783. Unpublished study prepared by E.I. Du Pont de Nemours and Company, DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, Delaware. April 27, 2011. MRID 48499406.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 48499406), a group of five male and five female Crl:CD(SD) rats was exposed by nose-only inhalation for 4 hours to ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] as aerosolized dust at a mean gravimetric concentration of 5.1 mg/L, with mean MMAD of 2.55 microns and GSD of 2.2. Exposure was on day 0, and the animals were observed for 14 days. The animals were approximately 9 weeks old (males: 291-345 g; females: 195-229 g) and supplied by Charles River Breeding Laboratories (Raleigh, North Carolina).

There were no deaths or treatment-related gross necropsy findings, and all of the animals gained weight during both weeks of the study. Treatment-related clinical signs included red nasal discharge from all animals and red ocular discharge from one female, which were noted upon removal from the exposure tubes and resolved by days 1-2. Two males and four females lost weight during days 0-1, but all of the animals gained weight over the remaining measuring intervals and had net body weight gains over days 0-7 and 7-14.

LC_{50} Males > 5.1 mg/L
LC_{50} Females > 5.1 mg/L
LC_{50} Combined > 5.1 mg/L

Based on the four-hour inhalation exposure LC_{50} for males, females, and the combined sexes, Imazapyr 75SG is in EPA Toxicity Category IV.

This acute inhalation study is classified as Acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Mean Gravimetric Conc. (mg/L)	MMAD µm	GSD	Mortality/Number Tested		
				Males	Females	Combined
14.3	5.1	2.4-2.7	2.2	0/5	0/5	0/10

Test Atmosphere / Chamber Description: The test material was milled by the study sponsor to provide a suitable powder. The exposure atmosphere was generated by using a volumetric feeder (K-Tron model T-20, twin screw) to meter the test material to a jetmill (Fluid Energy Processing, model 00) supplied with compressed air by a controller. The resultant dust atmosphere was passed through a 1-Liter cyclone elutriator before entering the exposure chamber. The cylindrical, glass nose-only inhalation chamber had an internal volume of approximately 34 Liters and was constructed with an internal baffle to promote uniform distribution of the test atmosphere.

Gravimetric Conc. (mg/L)	5.1±1.3 (range: 3.4-6.7)
Chamber Volume (L)	34
Mean Total Airflow (L/min)	30
Temperature (° C)	19-20
Relative Humidity (%)	50-64
Time to T_{95} equilibrium (minutes)	3.4

Test atmosphere concentration: Gravimetric samples were collected at approximately 30-minute intervals during exposure (8 total samples), using a vacuum pump and pre-weighed glass fiber filters. Collections were carried out for 1 minute at an airflow of 2.3 L/min. The mass collected was then divided by the total volume of air sampled.

Particle size determination: Two samples were taken during exposure using a Sierra® series 210 cyclone preseparator/cascade impactor and a Sierra® series 110 constant flow air sampler at a sampling rate of 5.0 L/min. for a 1 minute duration. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined.

A. Mortality: There were no deaths.

B. Clinical observations: Upon removal from the exposure tubes, all animals had red nasal discharge, and one female also had red ocular discharge; these signs resolved by day 2. On day 14, one male had a skin sore on the dorsal neck area, which was not considered treatment-related. Two males and four females lost weight during days 0-1, but all of the animals gained weight over the remaining measuring intervals and had net body weight gains over days 0-7 and 7-14.

C. Gross Necropsy: The only abnormal finding was confirmation of the skin sore on the dorsal neck area of one male.

D. Reviewer's Conclusions: The four-hour exposure LC_{50} for males, females, and the combined sexes is greater than 5.1 mg/L. Based on these results, the test material is classified as EPA Toxicity Category IV.

E. Deficiencies: None.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; EPSL Reference No.: 101207-1D; Off-white solid; pH: ~5 (1% aqueous solution); expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Lowe, C. (2011) Imazapyr (DPX-A7586) 75SG: primary eye irritation study in rabbits. Study Number 31316. Unpublished study prepared by Eurofins PSL, Dayton, New Jersey. April 22, 2011. MRID 48499407.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 48499407), 0.1 mL (0.06 g) of ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] was instilled into the conjunctival sac of the right eye (anesthetized with 0.5% tetracaine hydrochloride solution) of one male and two female, young adult New Zealand albino rabbits, and the upper and lower lids were held shut for approximately one second. Eyes were scored for ocular irritation according to the Draize method at 1, 24, 48, and 72 hours and at 4 days after instillation, and fluorescein staining was done at 24 hours and as needed thereafter. The anesthetized but otherwise untreated left eye of each animal served as a control. The animals were supplied by Robinson Services Inc., Clemmons, North Carolina (male: 2.58 kg; females: 2.16-2.23 kg); exact ages of the animals were not provided.

There were no observations of iritis. Corneal opacity (score=1 and affecting one quarter or less of the surface) was noted in one eye at 1 hour, in three eyes at 24 hours, in two eyes at 48 hours, and in one eye at 72 hours after instillation, with all eyes clear of corneal opacity at 4 days. At 1 hour after instillation, all three treated eyes had conjunctival redness, chemosis, and discharge (scores=2, 1-2, and 2-3, respectively); thereafter the incidence and severity of the conjunctival findings generally decreased over time, such that no "positive" conjunctival effects were present at 72 hours, and all eyes were clear of conjunctivitis at 4 days. No abnormal systemic clinical signs were recorded. The maximum mean total score (MMTS) was 13.7, recorded at one hour and at 24 hours after test material instillation.

In this study, the formulation is mildly irritating. Imazapyr 75SG is classified as EPA Toxicity Category III for primary eye irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Observations	Number "positive"/number tested				
	Hours				Days
	1	24	48	72	4
Corneal Opacity	1/3	3/3	2/3	1/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3
Conjunctivae:					
Redness *	3/3	3/3	2/3	0/3	0/3
Chemosis *	2/3	1/3	0/3	0/3	0/3
Discharge**	3/3	1/3	0/3	0/3	0/3
Severity of Irritation: Mean Total Score [a]	13.7	13.7	8.7	3.0	0.0

* Score of 2 or more required to be considered "positive."

** Not considered a positive irritation effect; however, scores of 2 or greater are noted here for completeness.

[a] Calculated by Reviewer according to Draize.

A. Observations: There were no observations of iritis. Corneal opacity (score=1 and affecting one quarter or less of the surface) was noted in one eye at 1 hour, in three eyes at 24 hours, in two eyes at 48 hours, and in one eye at 72 hours after instillation, with all eyes clear of corneal opacity at 4 days. At 1 hour after instillation, all three treated eyes had conjunctival redness, chemosis, and discharge (scores=2, 1-2, and 2-3, respectively); thereafter the incidence and severity of the conjunctival findings generally decreased over time, such that no "positive" conjunctival effects were present at 72 hours, and all eyes were clear of conjunctivitis at 4 days. No abnormal systemic clinical signs were recorded.

B. Results: The maximum mean total score (MMTS) was 13.7, recorded at one hour and at 24 hours after test material instillation.

C. Reviewer's conclusions: The test material is mildly irritating to the eye and is classified as EPA Toxicity Category III for primary eye irritation.

D. Deficiencies: As a minor deficiency, the ages of the animals were not provided.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Primary Dermal Irritation - Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; EPSL Reference No.: 101207-1D; Off-white solid; pH: ~5 (1% aqueous solution); expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Lowe, C. (2011) Imazapyr (DPX-A7586) 75SG: primary skin irritation study in rabbits. Study Number 31317. Unpublished study prepared by Eurofins PSL, Dayton, New Jersey. April 22, 2011. MRID 48499408.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 48499408), three young adult, male, New Zealand albino rabbits were dermally exposed for 4 hours to 0.5 mL of ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] as a dry paste (75% w/w mixture) in distilled water. The doses were applied to intact, clipped, 6-cm^2 application sites on the trunk and covered by a 4-ply gauze pad secured with semi-occlusive 3-inch Micropore tape wrapped around the trunk. The animals were observed at 30-60 minutes and at 24, 48, and 72 hours and at 7 days after patch removal, and any irritation at the dose sites was scored according to Draize. The animals were supplied by Robinson Services Inc., Clemmons, North Carolina and weighed 2.08-2.41 kg; exact ages of the animals were not provided.

At 30-60 minutes after patch removal, two treated sites exhibited well-defined erythema (score=2) and very slight edema (score=1), and one treated site exhibited very slight erythema (score=1) with no edema. At 24 hours, well-defined erythema and very slight erythema were noted on one and two sites respectively, and very slight edema was noted on two sites. At 48 hours, very slight erythema was noted on two sites, and very slight edema was noted on one site. At 72 hours, very slight erythema was noted on one site, and at 7 days all sites were clear of erythema and edema. Desquamation was noted at one site at 72 hours and at 7 days. No abnormal systemic clinical signs were reported.

In this study, the Primary Irritation Index (PII) is 1.42, and the formulation is a slight irritant. Based on the absence of moderate erythema at 72 hours, Imazapyr 75SG is classified as EPA Toxicity Category IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary skin irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES [ERYTHEMA/EDEMA]

Animal No.	Sex	Hours				Days
		0.5 - 1	24	48	72	7
3501	M	1/0	2/1	1/1	1/0 [a]	0/0 [a]
3502	M	2/1	1/0	0/0	0/0	0/0
3503	M	2/1	1/1	1/0	0/0	0/0
Severity of Irritation - Mean Score		1.67/0.67	1.33/0.67	0.67/0.33	0.33/0.00	0.00/0.00

[a] Desquamation present at dose site.

A. Observations: At 30-60 minutes after patch removal, two treated sites exhibited well-defined erythema (score=2) and very slight edema (score=1), and one treated site exhibited very slight erythema (score=1) with no edema. At 24 hours, well-defined erythema and very slight erythema were noted on one and two sites respectively, and very slight edema was noted on two sites. At 48 hours, very slight erythema was noted on two sites, and very slight edema was noted on one site. At 72 hours, very slight erythema was noted on one site, and at 7 days all sites were clear of erythema and edema. Desquamation was noted on one site at 72 hours and at 7 days. No abnormal systemic clinical signs were reported.

B. Results: The PII is 1.42.

C. Reviewer's Conclusions: The test material is a slight irritant. The test material is classified as EPA Toxicity Category IV.

D. Deficiencies: As a minor deficiency, the ages of the animals were not provided.

Reviewer: Byron T. Backus, Ph.D. **Date:** November 7, 2011
Risk Manager (EPA): 25

STUDY TYPE: Dermal Sensitization – LLNA in Mouse; OPPTS 870.2600; OECD 429

TEST MATERIAL: Imazapyr 75SG; 75.36% (w/w) Imazapyr; Lot no.: DPX-A7586-042; Haskell Reference No.: 29912; off-white solid; expiration date: February 13, 2012; stored at room temperature; expected to be stable for the duration of testing.

CITATION: Hoban, D. (2011) Imazapyr (DPX-A7586) 75SG: local lymph node assay (LLNA) in mice. Study Number 31787. Unpublished study prepared by E.I. Du Pont de Nemours and Company, DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, Delaware. April 20, 2011. MRID 48499409.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 48499409), groups of five female CBA/JHsd mice were treated with ground Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042] in N,N-dimethylformamide (DMF) at concentrations of 0% (vehicle only), 5%, 25%, 50%, or 80% applied to the dorsal surface of both ears (25 µL per ear), once daily on three consecutive days (days 0-2), and an additional group of animals was treated in identical manner with a 25% dilution of alpha-hexylcinnamaldehyde in N,N-dimethylformamide. On day 5, the mice were injected with phosphate buffered saline containing ^{3}H-methyl thymidine and then were killed five hours later. The draining (auricular) lymph nodes were excised, and incorporation of ^{3}H methyl thymidine was measured by liquid scintillation counting. The animals were approximately 9 weeks old, weighed 21.1-25.1 g, and were supplied by Harlan Sprague Dawley (Frederick, Maryland).

None of the mean stimulation indices of the treated groups were more than 3-fold greater than that of controls, whereas, the mean stimulation index of the concurrent positive controls was 5.41. No treatment-related effects on body weight or abnormal systemic clinical signs were seen. All of the mice in the 50% and 80% concentration groups had staining of the skin/fur of the ears.

Based on this study, Imazapyr 75SG is *not* a dermal sensitizer.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 429) in the mouse.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

MATERIALS AND METHODS:

A. Vehicle and positive control: The vehicle was N,N-dimethylformamide. The positive control was a 25% solution of alpha-hexylcinnamaldehyde in N,N-dimethylformamide.

B. Treatment preparation and administration: On days 0, 1, and 2, the vehicle control, positive control, or the appropriate dilution of the test material was applied to the dorsal surface of both ears (25 µL per ear) using an adjustable pipette. On day 5, the mice were injected with an unspecified

volume of phosphate-buffered saline (PBS) containing ^{3}H-thymidine (20 μCi to each mouse). Approximately five hours later, animals were killed, and the draining (auricular) lymph nodes were excised. A single cell suspension of lymph node cells was prepared for each animal and incubated overnight at 2-8° C. The incorporation of ^{3}H-methyl thymidine was measured by liquid scintillation counting.

RESULTS AND DISCUSSION:

A. Disintegrations per minute (group means):

Concentration %	Animal Number	Individual Animal DPM	Group Mean DPM	Stimulation Index (SI)
0 (Vehicle)	101	276	919.6±482.95	1.0
	102	1571		
	103	668		
	104	1015		
	105	1068		
5	201	885	1351.0±449.95	1.47
	202	1122		
	203	1784		
	204	1881		
	205	1083		
25	301	1370	1366.8±497.75	1.49
	302	1178		
	303	915		
	304	2209		
	305	1162		
50	401	3493	1931.0±994.67	2.10
	402	1809		
	403	2123		
	404	856		
	405	1374		
80	501	1591	1471.0±193.07 *	1.60
	502	1465		
	503	1190		
	504	1410		
	505	1699		
Positive Control	601	3826	4973.8±1243.87	5.41
	602	3812		
	603	5241		
	604	6821		
	605	5169		

Stimulation Index = Group Mean DPM ÷ Vehicle Control Mean DPM

* Significantly different from vehicle control ($p<0.01$)

B. Stimulation Index:

Sample Description Test or Control	Vehicle	5%	25%	50%	80%	Positive Control
Stimulation Index	1.0	1.47	1.49	2.10	1.60	5.41

C. Reviewer's conclusions: In agreement with the study author, the results of this study were not consistent with dermal sensitization. None of the mean stimulation indices of the treated groups were more than 3-fold greater than that of controls, whereas, the mean stimulation index of the concurrent positive controls was 5.41.

D. Deficiencies: The study report did not include full details of the test conditions, including the details of the dosing formulation preparation and the manner in which the dose preparations were applied.

ACUTE TOX ONE-LINERS:

1. DP BARCODE: 390860				
2. PC CODE: 128821				
3. CURRENT DATE: August 9, 2011				
4. TEST MATERIAL: Imazapyr 75SG [75.36% (w/w) Imazapyr; Lot #DPX-A7586-042]				
Study/Species/Lab Study # /Date	**MRID**	**Results**	**Tox. Cat.**	**Core Grade**
Acute oral toxicity / rat Eurofins PSL Study #31314 / April 22, 2011	48499404	LD_{50} Females >5000 mg/kg	IV	A
Acute dermal toxicity / rat Eurofins PSL Study #31315 / April 22, 2011	48499405	LD_{50} Males > 5000 mg/kg LD_{50} Females: > 5000 mg/kg LD_{50} Combined > 5000 mg/kg	IV	A
Acute inhalation toxicity / rat E.I. du Pont de Nemours and Company Study #31783 / April 27, 2011	48499406	LC_{50} Males > 5.1 mg/L LC_{50} Females > 5.1 mg/L LC_{50} Combined > 5.1 mg/L	IV	A
Primary eye irritation / rabbit Eurofins PSL Study #31316 / April 22, 2011	48499407	Mildly irritating; MMTS=13.7 at 1 hour and 24 hours	III	A
Primary dermal irritation /rabbit Eurofins PSL Study #31317 / April 22, 2011	48499408	Slight irritant; PII=1.42;	IV	A
Dermal Sensitization /mouse E.I. du Pont de Nemours and Company Study #31787 / April 20, 2011	48499409	*Not* a sensitizer	--	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived